REMARKS

Claims 1, 14, 16 and 18 are pending in the instant application. Claims 1, 14, 16 and 18 have been rejected. Claim 1 has been amended. Claims 16 and 18 have been canceled. No new matter has been added by this amendment. Reconsideration is respectfully requested in light of the following remarks.

I. Non-Compliance of Previous Response

The Examiner suggests that the response filed September 1, 2005 is not compliant with the rules set forth under 37 C.F.R. §1.121, since the listing of claims does not show each and every change that has been made to claim 16 relative to the preceding version.

The comma replacing the period in claim 16 was an inadvertent typographical error. However, in light of the cancellation of claim 16 herein, correction of this error is moot.

II. Objection to the Specification

The specification remains objected to for failing to demarcate trademarks such as GenBank™ and Tween™. The Examiner has required appropriate correction. Applicant has amended the specification to include these trademarks and therefore respectfully requests that this objection be withdrawn.

The specification also remains objected to for the impermissible referral to embedded hyperlinks and/or other forms of browser-executable code, and to the Internet contents so identified. The Examiner has required deletion of reference to identified internet contents at page 86. Applicant has removed

reference to the webpage index at the cancer.org website and therefore respectfully requests that this objection be withdrawn.

III. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 1, 14, 16 and 18 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicant's arguments filed September 1, 2005 were not found persuasive. It is suggested that the use of the claimed invention would not be reasonably enabled by the instant specification, as the skilled artisan could not do so without first establishing the role of BMP-2 in lung cancer, determine whether or not its inhibition would be clinically advantageous, and if so, identifying and making a suitable inhibitor of BMP-2 activity the comprises noggin, such that tumor vascularization is reduced and the patient clinically benefits from the treatment. The Examiner suggests that as evidenced by Langenfeld et al. (2003) and Langenfeld et al. (2004), the amount of guidance, direction and exemplification is not sufficient to enable such use of the claimed invention. It is suggested that there is paradoxical, conflictive results reported in the literature, which indicate the role of BMP-2 in cancer is not well enough understood to permit reasonable use of the claimed invention without first performing additional undue and unreasonable experimentation to establish its role and determine if inhibiting its activity will provide therapeutic benefit to patients diagnosed with cancer. As evidenced by the teachings of Gura (of record), Bergers (of record), Schuh ((2004) *Toxicologic Reports* 32:53-66), Bibby ((2004) *Eur. J. Cancer* 40:856-857), and Peterson, et al. ((2004) *Eur. J. Cancer* 40:837-844), the Examiner

also suggests that there is a common lack of extrapolation of results of studies performed *in vivo* using mouse models to accurately and reliably predict the effects of the same treatments of human patients, whereas other models such as orthotopic models are more clinically relevant. It is also suggested the despite the finding disclosed in the instant application that co-injecting mouse noggin and A549 lung cancer cells slows or reduces the formation and vascularization of tumors in immunocompromised mice, it is disturbing that contacting A549 lung cancer cell line with noggin *in vitro* promotes, rather than inhibits the growth of cells. Further, it is suggested that because the working example shows reducing the growth and vascularization of lung cancer cells by co-injecting tumor cells and mouse noggin into a mouse, this example does not exemplify the use of the claimed invention, namely a method for treating a pre-established tumor in humans. The Examiner further suggests that the disclosure does not provide sufficient guidance and direction to enable the use of the claimed invention to treat a genus of tumors that overexpress BMP-2 or the use of gene therapy for treatment. Applicant respectfully disagrees with this rejection.

At the outset, Applicant respectfully disagrees with the Examiner's suggestion that a role for BMP-2 must be established before the therapeutic benefit of noggin can be realized. There is no such requirement for meeting enablement. What is required is that the disclosure, when filed, contains sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art *to make and use* the claimed invention. MPEP 2164.01. In this regard, Applicant has

established that a correlation exists between the overexpression of BMP-2 in a lung tumor and the use of a BMP-2 activity inhibitor such as noggin to reduce vascularization of such a lung tumor. Applicant's own publications published in 2003 and 2004 support this finding by showing that *in vivo* lung tumor growth is inhibited by BMP-2 antagonists. Accordingly, in an earnest effort to highlight this feature of the present invention, Applicant has amended to claims to indicate that the BMP-2 overexpressing tumor is a lung tumor. Support for this amendment is found throughout the specification and in particular in the Examples of the specification.

Moreover, in meeting the enablement requirement, Applicant has used a *bona fide in vivo* animal model for lung cancer and demonstrated that noggin reduces vascularization of lung tumors *in vivo*. The use of human A549 mouse xenografts for evaluating therapeutic efficacy of drugs for treating lung cancer is well-established in the art. For example, Sirotnak et al. ((2000) *Clin. Cancer Res.* 6:4885-92; abstract enclosed herewith) teach that co-administration of ZD1839 with cytotoxic agents is highly effective at regressing A549 tumors in mice. In phase I clinical trials with this same drug (*i.e.*, ZD1839), toxicity was manageable and clinical responses were observed in patients with various malignant tumors, in particular non-small cell lung cancer (see Meric et al. (2000) *Bull. Cancer*. 87(12):873-6; abstract enclosed herewith). Thus, Applicant has provided an *in vivo* animal model example in the specification, which one of skill in the art would readily recognize as a working example commensurate in scope with the amended claims. MPEP 2164.02 states that if the art is such that a particular model is

recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate.

The Examiner has provided no such evidence with respect to the disclosed *in vivo* animal model. What has been provided is a general commentary on the use of *in vivo* mouse models (*e.g.*, Schuh, Bibby, Peterson), references pertaining to cancers other than lung cancer (*e.g.*, Hardwick, et al., Haramis, et al., Nishanian et al., Ghosh-Choudhury et al., Tomari et al., Nakamura et al., and Wen et al.), and *in vitro* results of BMP-2 suppression of A549 lung cancer cells (*e.g.*, Tada et al. and Buckley et al.). Unlike the teachings of Tada and Buckley, Applicant has placed lung tumor cells under the complex conditions of the *in vivo* environment, wherein the cells are subjected to various growth factors and cell-to-cell contact. Without this *in vivo* context, the teachings of Tada and Buckley can not be held to contradict the instant results.

As shown in Figure 10, Applicant has demonstrated that by co-injecting noggin with lung cancer cells, lung tumor growth and vascularization can be reduced thereby providing benefit to a patient at risk of developing a lung tumor. Accordingly, in an earnest effort to impart these novel findings, Applicant has amended the claims to indicate that the subject being treated is at risk of developing a lung tumor. Support for this amendment is found at page 8, paragraph [**0025**], which indicated that in the therapeutic aspects of the present invention, the BMP-2 activity inhibitor is administered to "a patient to treat tumors or to treat the risk of developing tumors in a patient by decreasing vascular development and/or angiogenesis." Accordingly, the

disclosed example exemplifies the use of the claimed invention, namely a method for preventing vascularization of a lung tumor in humans.

In an earnest effort to facilitate the prosecution of the claims 1 and 14, drawn to the use of noggin protein, Applicant is canceling claims 16 and 18, reserving the right to file continuing applications for the canceled subject matter.

Accordingly, given that Applicant has provided a disclosure which contains sufficient information regarding the subject matter of the claims and further provided a working example commensurate in scope with the claims, one skilled in the pertinent art could readily make and use the claimed invention. It is therefore respectfully requested that this rejection be reconsidered and withdrawn.

IV. Conclusion

The Applicant believes that the foregoing comprises a full and complete response to the Office Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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